

Stimulants--Cholinergic Drugs

Acetyl Choline

Acetylcholine is the chemical transmitter for nerves of the parasympathetic, somatic, preganglionic sympathetic, and parts of the central nervous system. Acetylcholine is synthesized by the transfer of an acetyl group from acetyl CoA to choline, a normal constituent of the diet.

Acetylcholine and other Agonists

Synthesis of Acetylcholine

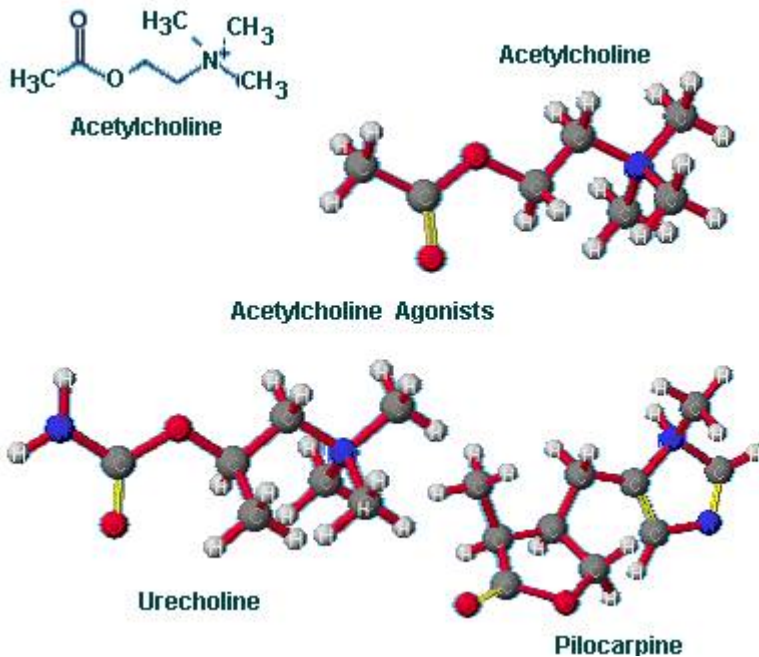


Acetylcholine is concentrated in large amounts in **presynaptic** vesicles, which release their contents into the synapse when voltage-gated calcium channels open in response to membrane depolarization. Upon interaction with the receptor, acetylcholine produces an influx of sodium through a ligand-gated ion channel which sends the impulse.

After acetylcholine interacts with the cholinergic receptor it is very rapidly hydrolyzed by the enzyme acetylcholinesterase. The hydrolysis reaction is the reverse of the synthesis reaction except that choline and acetic acid are products. The choline is retaken up by the nerve ending where it is reused for synthesis of new molecules of acetylcholine.

Acetylcholine acts on two vastly different classes of receptors - nicotinic receptors (with two subtypes, one at the neuromuscular junction of skeletal muscle, the other within ganglia and the CNS), and muscarinic receptors (widely distributed within both peripheral and central nervous systems). Muscarinic receptors originally were distinguished from nicotinic receptors by the selectivity of the agonists muscarine and nicotine respectively. Notice the similarities in structure for all three of these compounds.

Although there appears to be at least two cholinergic receptor sites, they are similar enough to be considered as one. The acetylcholine interacts with the receptor site through ionic attraction of the positive nitrogen, polar attraction of the ester group, and through hydrophobic interactions with the methyl groups.

**Stimulation:**

Stimulation of cholinergic nerves is achieved either directly or indirectly. Direct acting agents (agonists) activate the receptor site by mimicking the effects of acetylcholine. Cholinesterase inhibitors act indirectly by preventing the enzyme from hydrolyzing (inactivating) acetylcholine at the receptor site. This inhibition permits the buildup of acetylcholine and results in more intensive and prolonged activation of the receptor site. The effects of cholinergic stimulation include: vasodilation of blood vessels; slower heart rate; constriction of bronchioles and reduced secretion of mucus in the respiratory tract; intestinal cramps; secretion of saliva; sweat and tears; and constriction of eye pupils.

Direct Acting Cholinergic Agents - Agonists:

Direct acting cholinergic agents act as agonists and initiate stimulant type responses at the receptor site. Direct stimulation of acetylcholine receptors is achieved by: Arecholine, Pilocarpine, Urecholine (Betanecol), Carbachol, Choline, Metacholine, Mushrooms (*Boletus* sp., *Clitocybe* sp., *Inocybe* sp.)

Drugs: Urecholine and pilocarpine are direct acting drugs. Urecholine is used to restore parasympathetic tone to smooth muscles of the intestinal tract and bladder following abdominal surgery. Pilocarpine is used to constrict pupils and reduce pressure caused by glaucoma. Pilocarpine contracts the ciliary muscle which causes the iris to be withdrawn. This action permits drainage of the aqueous humor and thus relieves the pressure due to a glaucoma condition.

Cholinergic Poison agents which mimic the structure of acetylcholine include two poisons: **muscarine** - an alkaloid present in poisonous mushrooms and **nicotine** from cigarettes. Muscarinic effects are those of parasympathetic overactivity and include bradycardia, pinpoint pupils, sweating, blurred vision, excessive lacrimation, excessive bronchial secretions, wheezing, dyspnoea, coughing, vomiting, abdominal cramping, diarrhea, and urinary and fecal incontinence.

Nicotine: Nicotinic effects are those of sympathetic overactivity and neuromuscular dysfunction and include tachycardia, hypertension, dilated pupils, muscle fasciculation and muscle weakness.

Accidental ingestion of these poisons may produce death from heart failure unless treated with a suitable antidote. Atropine blocks the receptor site to decrease the stimulant effects produced by the muscarine type poisons, but has no effect on nicotine receptors.